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6 May 2004

Division of Dockets Management (HFA-305) Food and Drug Administration 5630 Fishers Lane, Room 1061 Rockville MD 20852

Re: Docket No. 2003D-0553: Draft Guidance for Industry on Vaccinia Virus –
Developing Drugs to Mitigate the Complications Associated with Vaccinia
Virus Used for Smallpox Vaccination

Dear Sir or Madam;

Chimerix, Inc. welcomes the opportunity to submit comments on the FDA's draft guidance regarding the development of drugs to treat complications that may occur from smallpox vaccination with vaccinia virus. Chimerix appreciates and supports the FDA's efforts to provide guidance to sponsors for planning and designing appropriate nonclinical and clinical studies for such drugs. We offer the following comments and requests for clarification for your consideration.

# Section III.B. Drugs with previous or Concurrent Studies for Other Indications (lines 204-211)

**Draft Guidance** – This section indicates that if the drug under evaluation is currently under study or has had approval sought for a non-vaccinia indication, the applicant may not need to collect as much additional data to complete the safety database.

**Comments** – Chimerix concurs with this proposal, but requests clarification on the extent to which historical safety data for an approved drug can be used to expedite development when the approved drug is chemically modified (*e.g.*, prodrugs) to enhance bioavailability of the active moiety.

### Section III.D. 1. Timing of Nonclinical Studies to Support the Conduct of Human Clinical Trials (lines 307 – 310)

**Draft Guidance** – This section indicates that toxicology studies should be carried out to support the safety of administration of the drug for at least 2 weeks in humans.

Comments – Chimerix appreciates the need to complete toxicology studies of sufficient duration to support clinical trials. As stated in FDA's Guidance for Industry: Single Dose Acute Toxicity Testing for Pharmaceuticals (1996) and reiterated in ICH M3:

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Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (1997), single-dose toxicity studies with extended examinations in a rodent and a nonrodent species are considered by FDA to be sufficient to support an initial single-dose clinical trial. The subject draft guidance should clarify whether single-dose toxicity studies could be sufficient to support an initial single-dose clinical trial for drugs intended to treat complications of vaccinia smallpox vaccine.

### Section III.D.5. Reproductive Toxicity (Lines 371 – 375)

**Draft Guidance** – In this section, FDA expresses an expectation that certain nonclinical studies for detecting toxicity to reproduction be completed prior to early studies in healthy volunteers and that all nonclinical studies for detecting toxicity to reproduction be completed prior to administration of the drug to patients.

Comments - This expectation is inconsistent with ICH M3: Guidance on Nonclinical Safety Studies for Conduct of Human Clinical Trials for Pharmaceuticals. ICH M3 states that "In the United States, women of childbearing potential may be included in early, carefully monitored studies without reproduction toxicity studies provided appropriate precautions are taken to minimize risk." The ICH guidance also states that studies of the effects of a drug on embryo-fetal development and fertility should be completed prior to Phase 3. We request clarification on why FDA believes that nonclinical studies for detecting toxicity to reproduction are needed earlier in the clinical development program for drugs intended to treat complications of vaccinia smallpox vaccine.

# Section III.E.1 Nonclinical Virology Reports (lines 407 – 408) and Section III.E. 2.g. Selection of Resistant Virus In Vitro (lines 527 – 532)

**Draft Guidance** – In these sections FDA describes nonclinical virology studies that should "be well advanced or completed prior to the introduction of the candidate drug into humans," including alternative methods for isolating virus with reduced susceptibility to the candidate drug via propagation for several passages.

Comments – Isolating virus with reduced susceptibility to a drug can require a significant number of passages and substantial time. If the efficacy of a candidate drug will be studied in animal models rather than clinical trials (*i.e.*, in accordance with 21 CFR part 314, subpart I) and safety data will be obtained from non-vaccinated healthy volunteers, it would seem unnecessary to delay the initiation of Phase 1 clinical trials until data are available on the potential of vaccinia to develop drug resistance. We request clarification on the rationale for requiring pre-IND information on the potential for vaccinia resistance to the candidate drug.

#### Section V. Clinical Data

**Draft Guidance** – This section describes considerations for potential clinical trials in patients receiving vaccinia vaccination either through a non-emergent vaccination program or in the event of a variola bioterrorism attack.

Comments – The guidance is silent on the opportunity to evaluate a candidate drug for treating complications of vaccinia vaccination within the context of a vaccine trial. Although it is generally undesirable to evaluate two investigational products in the same clinical trial, there are likely to be limited opportunities to study both smallpox vaccines and drugs for the treatment of vaccine complications. To ensure efficient and timely development of both types of products, industry and government must be willing to consider unique clinical trial designs. We request that the FDA provide in the guidance a discussion of trial designs that include both an investigational vaccine and an investigational drug to treat vaccine complications.

We are pleased to have the opportunity to provide our comments on the draft guidance. For inquiries regarding our comments, please contact me by telephone at (919) 806-1074, ext 106, by facsimile at (919) 806-1146, or by e-mail at mdoucette @chimerix-inc.com.

Sincerely,

Marna Doucette

Director, Regulatory Affairs